4里 9克 8日; 8日40分;农市屋大学医学8层一生化学

X19"1 10"97" #1011# 2/ 8

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## In the united states patent and trademark office

Applicant:

Takashi MURAMATSU et al.

Title:

Barly Career Tumor Marker

Appl. No.:

10/070,5(9

Filing Date:

March 8, 2002

Examiner:

Alana M. HARRIS

Art Unit:

1642

MAIL STOP AF
Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

## DECLARATION UNDER 37 C.F.R. § 1.132

- I, Kenji Kadomatsui do hereby make the following declarations:
- 1. After obtaining my med cal license in 1982, I worked for two years as a Pediatric Surgeon at the Fukuoka Children's Hospital and Kyushu University Hospital in Kyushu, Japan. In 1989, I obtained my Ph.D. from the Kyushu University Graduate School of Medicine. It was charing these years of my graduate studies that I discovered a noval growth factor called "Midkine". Ever since this discovery, I have dedicated my research to clucidating the characteristics and finctions of Midkine and its potential therapeutic values in various diseases, including cano. For more details of my educational and professional qualifications, please see my curriculum vitae attached hereto as Exhibit 1.
- I am a co-author of the iduraments et al. article published in 1996 in the Journal of Biochemistry, vol. 119, p. 1171-1175 (hereinafter, Murameteu et al.).
- 3. I have reviewed the above identified U.S. patent application (U.S. Serial No. 10/070,569 hereinafter, the '569 application) as originally filed as well as claims 1-9 and 13-16 as amended becawith.
- 4. I have reviewed the office action of March 9, 2004, particularly the rejection of claims 1,
- '4, 5, 8, and 9 under 35 USC \$ 102(b) as being anticipated by Muramatsu et al. and the

CIA40307-Declaration.doc

4年 8月 8日; 3劳42分;古古是大学医学思维一生化学

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Serial No. 10/070,569

Declaration of Dr. Kenji Kacomatsu

rejection of claims 1, 4, 5, 8, 9, and 13 under 35 USC § 103(a) as being obvious in view of Muramaten et al.

- 5. As a co-surface of the Muramatsu et al. reference, I am quite familiar both with the scope of disclosure and the state of the art at the time of publication. With regard to this Muramatsu et al. paper, based on my experiences from the discovery of Midkine to the launching and supervision of flurther Midkine-related studies, I recognized (i) the impurtance of this resea th with regards to forming a basis for the clinical application of midkine, and (ii) provide d MEP-MK (a fusion protein of maltose-binding protein and midkine) as a fundament at tool casemial to affinity columns for purifying anti-midkine antibodies.
- 6. It is my understanding that the Examiner believes that, since Muramatan et al. did not disclose that the patients studied suffered from hepatocalhilar carcinoma that was metastatio, the reference is regarded as disclosing or suggesting a method of detecting "early cancer", i.a., cancer confined to the site of development. However, it is important to note that a cancer that has not metastasized is not necessarily an "early cancer", as that term is defined in the ins ant specification (i.e., a cancer categorized as stage 0 or stage 1 of the TNM classification i); equally, a cancer that has metastasized is not necessarily an advanced cancer as that erm is commonly understood. Accordingly, contrary to the Examiner's suggestion, it tere is no direct relationship between a cancer not metastasizing and that cancer being an sarry cancer. In other words, one skilled in the art cannot reasonably predict the stige of a cancer (i.e., stage 0, I, II, III, etc.) based on the presence or absence of metastasses alone.
- 7. Furthermore, upon information and belief, it is my opinion that Murametsu et al. does not contain an inherent or establing disclosure of the presently claimed invention. Specifically, Murametsu et al. did not classify the experimental samples according to cancer stage because, at the time the aperimental described in the reference were conducted, a protein that was accreted into the serum of satiy cancer patients (i.e., patients categorized at stage of or stage I of the TNM plassification), and thereby had the potential of becoming a simple and efficient marker for samples derived from early cancer, was virtually non-axistent. Since no one thought that reference, was surprised by stage cancer patients would yield positive results, no attempt among cancer stages. Even I, an author of the Murametsu et al. by the present invention's discovery, that MK is secreted into the serum of carry cancer patients with liver call cancer, it does not necessarily flow that one could predictably us MK for detecting early cancer because, at the time this reference was published, it was the general view that finding markers for early cancer was virtually

4至 8月 8日: 9時44分:石台港大學等中國一生企業

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Serial No. 10/070,569 Decisration of Dr. Kenji Kadomatsu

## impossible,

- 8. Since, at the time of publication of the Muramatau et al. reference, it was commonly believed that cancer man are were not present in the serum of early cancer patients, those skilled in the prior art we uld neither have predicted nor expected the positive MK serum samples to have been derived from patients with early cancer. In fact, only by analyzing a number of samples from patients of various early cancers were the present inventors able to conclusively demonstrate that MK is indeed an entremely affective marker for accoming and detecting early cancer.
- In light of the above, it is my opinion that the invention of pending claims 1, 4, 5, 8, 9, and
   is neither anticipated for rendered obvious by the Muramatsu et al. reference.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent lessing thereon.

K. Kadomatan

Rv

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Dated: September 8, 2004